bonding a second nucleotide having at least one protected chemical functional group to a deprotected chemical functional group of the nucleotide bonded molecule or said other deprotected molecule; and

repeating the selective deprotection of a chemical functional group on a protected bonded nucleotide or a protected bonded molecule and the subsequent bonding of an additional nucleotide to said deprotected chemical functional group until at least two separate oligonucleotides of desired length are formed on the substrate surface wherein during said selective deprotection steps, an electric potential is applied to one or more selected electrodes sufficient to generate electrochemical reagents at the selected electrodes capable of deprotecting the chemical functional groups on said proximate molecules or nucleic acids.

Please cancel claim 42 without prejudice.

Please cancel claim 43 without prejudice.

Please cancel claim 48 without prejudice.

Please cancel claim 49 without prejudice.

Please cancel claim 50 without prejudice.

Please cancel claim 51 without prejudice.

REMARKS

Claims 1, 3-9, 11-16, 22-41 and 44-47 are pending in the present application. Claims 2, 10, 17-21, 42-43 and 48-51 are cancelled herein without prejudice to the subject matter described thereby. The Examiner rejects all of the pending claims under either 35 U.S.C. §102 or under §101 based upon double patenting. Applicant herein changes the claim language of all claims rejected based upon double patenting. Specifically, Applicant cancels claim 2 and changes the dependency of claims 3-5 to depend from claim 1 instead of claim 2. Applicant changes claims 16 and 41 to remove the recitations regarding a buffering or scavenging solution. Finally, Applicant cancels claims 18-21, 43 and 48-51 since these claims define specific features of a buffering or scavenging solution.

Claim Objections

The Examiner objects to claim 10 under 37 CFR 1.75 as being a duplicate of claim 9. Applicant herein cancels claim 10 without prejudice. This objection is hereby obviated.

Rejection under 35 U.S.C. §102

The Examiner rejects claims 1-24, 27-33 and 36-40 as anticipated by Heller *et al.*, U.S. Patent No. 5,929,208. The Examiner sets forth the following reasons for the rejection:

The Examiner rejects claim 1 because Heller *et al.* allegedly disclose a method for electrochemical placement of a material at a specific location on a substrate, which comprises the steps of: providing a substrate having at its surface at least one electrode that is proximate at least one molecule bearing at least one protected chemical functional group (citing Column 17, lines 7-11); applying a potential to said electrode sufficient to generate electrochemical reagents capable of deprotecting at least one of the protected functional groups of said molecule and bonding the deprotected chemical (citing Column 20 lines 25-48).

The Examiner rejects claims 2 and 18 because Heller *et al.* allegedly disclose placing a buffer solution in contact with the electrode at the surface of the substrate to prevent electrochemically generated reagents from leaving the locality of the electrode (citing Column 22, lines 25-37).

The Examiner rejects claims 3 and 19 because Heller *et al.* allegedly disclose using a phosphate buffer (citing Column 22, line 41).

The Examiner rejects claims 4 and 20 because the prior art allegedly discloses that the buffering solution is present in a concentration of at least 0.01 mM (citing Column 22, line 40).

The Examiner rejects claims 5 and 21 because the prior art allegedly discloses that the buffering solution is present in a concentration range of 0.1 to 100 mM (citing Column 22, line 40).

The Examiner rejects claim 6 because Heller *et al.* allegedly disclose protected monomers or preformed molecules having protected chemical functional groups at non-bonding sites (citing Column 15, lines 48-58).

The Examiner rejects claims 7 and 22 because the prior art allegedly further discloses amino acid as the monomer (citing Column 21, line 30 and Column 6, lines 24-41).

The Examiner rejects claims 8 and 37 because Heller *et al.* allegedly employ pre-formed molecules selected from the group consisting of proteins, nucleic acids, polysaccharides and porphyrins (citing Column 17, lines 1-7 and Column 6, lines 24-41).

The Examiner rejects claims 9 (and duplicate claim 10) and 23 because Heller *et al.* allegedly disclose using linker molecules or monomers (citing Column 21, lines 10-16).

The Examiner rejects claims 11 and 24 because the molecule of Heller *et al.* is allegedly directly attached to the surface of the substrate via a linker molecule or attached to a layer of material overlaying the substrate (citing Column 14, lines 56-67).

The Examiner rejects claims 12 and 27 because Heller *et al.* allegedly teach protecting the chemical functional groups with an acid or base labile protecting group.

The Examiner rejects claims 13, 14, 29-31 and 40 because Heller *et al.* allegedly teach using an array of electrodes (citing Column 4, lines 44-54).

The Examiner rejects claim 15 because the combinatorial synthesis method of Heller *et al.* allegedly discloses sequentially deprotecting other protected chemical functional groups of the monomer or pre-formed molecule and bonding another monomer or pre-formed molecule to the deprotected monomer (citing Column 15, lines 48-58).

The Examiner rejects claim 16 because the method of Heller *et al.* allegedly further includes bonding a second monomer and repeating the selective deprotection of a chemical functional group (citing Column 20, lines 25-49).

The Examiner rejects claim 17 because Heller *et al.* allegedly discloses selective deprotection by the application of potential to one or more electrodes sufficient to generate electrochemical reagents at the selected electrodes.

The Examiner rejects claim 28 because the substrate used in the prior art allegedly may be a semiconductor, plastic, glass or ceramic substrate (citing Column 10, lines 5-8).

The Examiner rejects claim 32 as the microcapillary electrode tubes of Heller *et al.* allegedly have diameters in the range of 1-100μ (citing Column 22, lines 28-30).

The Examiner rejects claim 33 because Heller *et al.* allegedly teach using platinum electrodes (citing Column 14, lines 34-36).

The Examiner rejects claims 36 and 38 because Heller *et al.* allegedly teach additional bonding steps wherein pre-formed molecules are bonded to deprotected chemical functional groups, wherein the pre-formed molecule bear at least one protected chemical functional group (citing claims 6 and 8).

The Examiner rejects claim 39 because the electrode pads of Heller *et al.* allegedly are packaged with a switch box for selective activation (citing Column 25, lines 1-3).

Applicants explained some of the differences between the teachings of Heller *et al.* and the presently claimed invention in the present specification. Specifically, Applicant provided a summary of some of the differences at page 6, line 10 through page 7, line 12. Applicant explained that Heller *et al.* describe a self-addressable, self-assembling microelectronic system that can carry out controlled multi-step reactions in microscopic environments, including biopolymer synthesis of oligonucleotides and peptides. ***The Heller method employs free field electrophoresis to transport analytes or reactants*** to selected micro-locations where they are effectively concentrated and reacted with the specific binding entities. ***Each micro-location of the Heller device has a derivatized surface for the covalent attachment of specific binding entities, which includes an attachment layer, a permeation layer, and an underlying direct current micro-electrode.*** The presence of ***the permeation layer prevents any electrochemically generated reagents from interacting with or binding to either the points of synthesis or to reagents that are***

electrophoretically transported to each synthesis site. Thus, ***all synthesis is due to reagents that are electrophoretically transported to each site of synthesis.***

Applicant respectfully submits that one of the major differences of the presently claimed method over the method taught by Heller *et al.* is the presence of electrochemically generated reagents according to the present methods. Applicant respectfully directs the Examiner's attention to claims 1 and 47 where the recitation of this feature is explicit in the claim language. In the interest of further clarifying the present invention and thereby advancing prosecution, Applicant herein amends the other broadest pending claims, namely claims 16 and 41. Applicant herein combines the language of claims 16 and 17, and Applicant herein combines the language of claims 41 and 42. By way of this minor amendment, the broadest claims, namely claims 1, 16 and 41 now all recited the feature of electrochemically generated reagent. This feature is neither taught nor suggested by Heller *et al.* By explicitly reciting this feature in the claim language, Applicant clearly describes a method that is not anticipated by and that is not obvious over Heller *et al.* All of the remaining claims are patentable over Heller *et al.* for the simple reason that all the remaining claims depend from one of the independent claims among other reasons.

Applicant further set forth some of the limitations of the Heller *et al.* method and therefore some of the advantages of the presently claimed method. The method of Heller *et al.* is severely limited by the use of electrophoretic transport. First, electrophoretic transport requires that the reactants be charged in order to be affected by the electric fields; however, conventional reactants of interest for combinatorial chemistry are usually uncharged molecules not useable in an electrophoretic system. Second, the Heller method does not address the large amount of chemical crosstalk that inherently occurs because of the spatial distribution of the electric fields involved in the electrophoretic transport of the reagents for binding. In a system utilizing electrophoresis, one cannot use protecting groups to protect the reactive functional groups at the microlocations since there is no mechanism for removing the protective groups. The use of electrophoresis results in various binding entities and/or reactants being located throughout the solution used as they migrate, often coming into contact with unselected reaction sites. Thus, the combination of the lack of protecting groups and the spatial distribution of the electric fields inherent to electrophoresis allow such binding reactions to occur randomly, compromising the fidelity of any polymer being synthesized.

The presently claimed method provides an improved method for synthesizing a variety of chemical sequences at known locations that uses highly efficient deprotection and coupling mechanisms. The presently claimed method further provides a method for synthesizing a variety of chemical sequences at known locations that is cost-effective and practical. In addition, the presently claimed method allows using a smaller sized apparatus affording more efficient production in a specific area and time while maintaining the fidelity of the chemical sequences produced.

Double Patenting Rejection

The Examiner rejects claims 1 and 2, 3-5 and 16-51 over claims 1, 15-47 and 49-50 of U.S. Application Serial No. 09/003,075. Applicants herein change the claim language to delete the recitations regarding a buffering or scavenging solution. The specifics of such changes are described, *supra*. Therefore, the claims subject to this double patenting rejection no longer recite such a feature. Hence, the rejection based upon double patenting is obviated.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and earnestly seek rapid advancement as such. Should any questions arise in connection with this submission which may be resolved by a telephonic interview, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: June 9, 2000

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